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**The Rhox gene cluster suppresses germline LINE1 transposition.**

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**Public Summary:**

**Scientific Abstract:**

Transposable elements (TEs) are mobile sequences that engender widespread mutations and thus are a major hazard that must be silenced. The most abundant active class of TEs in mammalian genomes is long interspersed element class 1 (LINE1). Here, we report that LINE1 transposition is suppressed in the male germline by transcription factors encoded by a rapidly evolving X-linked homeobox gene cluster. LINE1 transposition is repressed by many members of this RHOX transcription factor family, including those with different patterns of expression during spermatogenesis. One family member-RHOX10-suppresses LINE1 transposition during fetal development in vivo when the germline would otherwise be susceptible to LINE1 activation because of epigenetic reprogramming. We provide evidence that RHOX10 suppresses LINE transposition by inducing Piwil2, which encodes a key component in the Piwi-interacting RNA pathway that protects against TEs. The ability of RHOX transcription factors to suppress LINE1 is conserved in humans but is lost in RHOXF2 mutants from several infertile human patients, raising the possibility that loss of RHOXF2 causes human infertility by allowing uncontrolled LINE1 expression in the germline. Together, our results support a model in which the Rhox gene cluster is in an evolutionary arms race with TEs, resulting in expansion of the Rhox gene cluster to suppress TEs in different biological contexts.

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